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Hyperuricemia as a Prognostic Marker for Severity of Illness in Sepsis

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Abstract: ***This was a prospective observational study conducted at shri Balaji institute of medical sciences with 100 ICU patients with diagnosis of Sepsis based on qSOFA score. Primary end point was to study association of hyperuricemia with mortality. Secondary end point was to study morbidity considering AKI, ARDS and duration of stay in the ICU.Once the patient met the inclusion criteria, consent was obtained and they were interviewed for demographic data such as age and sex, history of other comorbid conditions along with presenting complaints. Patients were subjected to physical examination. Blood samples obtained for uric acid, urea, creatinine, complete blood count, serum electrolytes, ABG and chest X-ray were done. Qualitative data was expressed in frequencies and percentages and Quantitative data in mean and standard deviation. Parametric tests include unpaired t test for intergroup comparison was used. Receiver operative curve (ROC) analysis was done to predict the cut off value of Uric acid to predict outcome. Sensitivity and specificity were calculated based on cut off values. Bar diagrams and pie chart were used to represent the data. p value of <0.05 was considered statistically significant. Results showed that 41% of sepsis patients presented with hyperuricemia (uric acid >6.8 mg/dl). Majority of hyperuricemia patients were between 51-70 years old, with notable male predominance. Hyperuricemia was significantly associated with comorbidities like coronary artery disease, stroke, liver disease, metabolic syndrome, and diabetes with Malignancy. Hyperuricemia was significantly linked to the development of Acute Kidney Injury (AKI), there was no statistically significant association was found with Acute Respiratory Distress Syndrome (ARDS), although a trend was observed. Hyperuricemia was significantly associated with prolonged ICU stays. Hyperuricemia significantly increased mortality risk, Out of 41% of hyperuricemia patients, 23 succumbing to complications, supporting its role as a strong predictor of mortality in sepsis. This research confirms the importance of uric acid as a prognostic biomarker in Sepsis. Elevated uric acid levels are associated with worse outcomes, including Prolonged ICU stays, increased risk of AKI, and higher mortality.***

Keywords: SIRS: Systemic Inflammatory Response Syndrome, CAD: Coronary Artery Disease AKI: Acute Kidney Injury, ARDS: Acute Respiratory Distress Syndrome,ICU: Intensive Care Unit, SOFA: Sequential Organ Failure Assessment MAP: Mean Arterial Pressure, WHO: World Health Organization,GBD; Global Burden of Diseases SE: Septic Encephalopathy, APACHE: Acute Physiology And Chronic Health Evaluation SAPS: Simplified Acute Physiology Score ,TISS: Therapeutic Intervention Scoring System LODS: Logistic Organ Dysfunction Score, MODS: Multiple Organ Dysfunction Score MEWS: Modified Early Warning Score,PRESEP: Prehospital Early Sepsis, PS: Acute Physiology Scorings: Glasgow Coma Scale, QSOFA: Quick Sequential Organ Failure Assessment ,EWS: Early ,Warning Score

1. Introduction

Sepsis is a life-threatening clinical condition with extensive physiological and Biochemical abnormalities. The Third International Consensus (Sepsis-3) Currently Defines sepsis as “organ dysfunction caused by a dysregulated host response to Infection”, emphasizing for the first time the crucial role of the innate and adaptive Immune response in the development of the clinical syndrome Septic shock is defined as a complication of sepsis resulting in derangements In circulatory and metabolic pathways in the body.

These patients can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

Cascade of reactions in Sepsis

- Hyper inflammation
- Activation of Complement system
- Activation of Coagulation and Vascular Endothelium
- Interaction between Complement and Coagulation Systems
- Endothelial Dysfunction
- Neutrophil Extracellular Traps

Majority of intensive care unit patients undergo ischemic-reperfusion injury and inflammation to varying degrees during their hospitalization. In the past 20 years, research has revealed that infection can cause multiple organ dysfunction but without a measurable inflammatory excess (i.e., without the Systemic inflammatory response syndrome [SIRS]). In fact, both pro- and anti-inflammatory Responses are present along with significant changes.

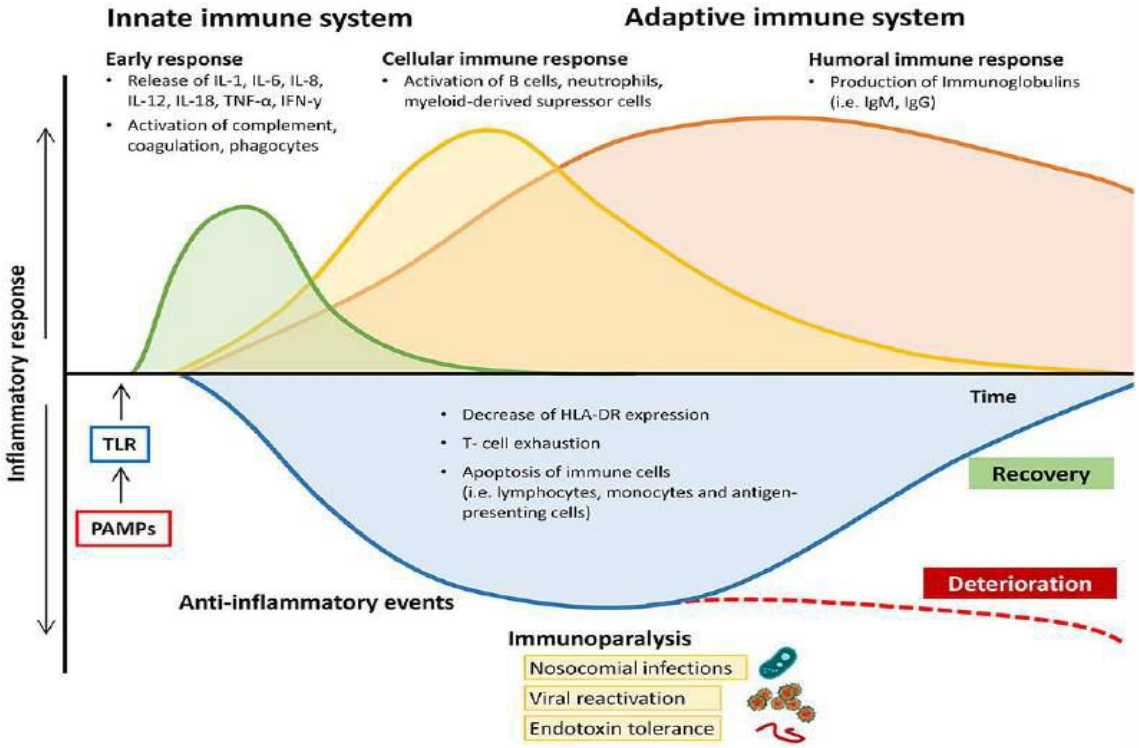


Figure 1: Changes in pro- and anti-inflammatory response of the immune system during the course of sepsis and septic shock. HLA-DR, human leukocyte antigen-D Related; IgM/G, immunoglobulin M/G; IL, interleukin; IFN-γ, Interferon γ; PAMPs, Pathogen-associated molecular patterns; TNF-α, tumour necrosis factor alpha; TLR, Toll like receptor. [2]

Biomarkers in sepsis

The diagnosis of infection is usually based on positive cultures or biomarkers of inflammation. However, microbiology results take several days to obtain and are Negative in up to one-third of cases, especially if antibiotics have been administered prior to culture. C-reactive protein (CRP) is the traditional marker of inflammation; it is elevated in a number of conditions besides infection, i.e. trauma, burns, and Pancreatitis. CRP synthesis in the liver is induced by interleukins and elevated levels are found within 6–8 hrs of introduction of a pathogen, with peaks after 36–50 hrs. [3] However, as mortality in sepsis rises with every hour of delayed effective treatment, there is great need for better early biomarkers. Presently, a plethora of promising biomarkers is emerging, but validity and Clinical utility has only been tested for very few of them. [9]

At present, the possible pathogenic mechanisms of hyperuricemia in sepsis are mainly as follows:

(1) RAAS is an important body fluid regulation system in the human body, which Maintains the body's metabolic cycle. However, uric acid enters endothelial cells Through organic ion transport, activates oxidative stress, up-regulates the expression of Angiotensin II, angiotensin receptors 1 and 2, and increases the binding of angiotensin II to the receptors, so that stimulating endothelial cells to produce intercellular cell Adhesion molecule-1, IL-1 and other inflammatory factors, which promotes the Senescence and apoptosis of endothelial cells. [5]

(2) Uric acid enters cells through uric acid transporter 1, reducing NADPH oxidase Activation, activating the RAAS system, and changing mitochondrial energy Metabolism to increase oxidative stress, leading to increased intracellular ROS and Promoting the expression of inflammatory mediators, thereby destroying proteins, Lipids, DNA and RNA to participate in a variety of cellular processes. [6]

(3) The hyperuricemia state can regulate the response of leukocytes to inflammatory Modes through epigenetic modifications (including histone methylation), which Promotes the release of pro-inflammatory cytokines such as IL-1b and IL-6, and reduce the release of IL-1Ra. When the serum uric acid exceeds the physiological Concentration, it is easy to form a kind of sodium urate crystals in the inner cells that Behaves as a pro-oxidant molecule, which is sensed by the immune system and promotes the inflammatory process of white blood cells. Uric acid crystals can induce Pro-inflammatory cytokines, such as IL-1b, increase the production of ROS, stimulate Chemotaxis, and activate NF-kB and mitogen-activated protein kinases pathways. [8]

Uric acid promotes mitochondrial modification of macrophages and increases the Production of ROS by mitochondria, and this metabolic change will promote the Activation of nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin Domain containing-3 (NLRP3) inflammasome and the production of IL-1b, and NLRP3

Is a key molecule that connects inflammation and cell metabolism to initiate? Inflammatory caspase and induce cell-death pathway. [9]So, level of serum uric acid could be used to predict the severity and prognosis of Septicaemia. Several studies had found that hyperuricemia can be used as a sign of poor Prognosis and mortality in patients with sepsis.

An explanation for the “double-faced Janus” of uric acid is provided by Sautin et.al. [8] Showing that uric acid is mainly

an antioxidant in hydrophilic environments such As plasma, and a pro-oxidant in hydrophobic environments such as the intracellular Environment. The fact that uric acid is a potent scavenger of singlet oxygen, peroxyl radicals, and hydroxyl radicals in hydrophilic environments such as plasma, but is unable to Supplement lipid-soluble radicals and prevent radical propagation in lipid membranes, Suggests that oxidative stress is common to all pathologies.[7]

Oxidative stress is found out by the presence of elevated serum uric acid which is a poor prognostic sign in case of patients with sepsis as multi organ dysfunction occurs as a result of high oxygen free radicals. Increased levels of serum uric acid Causes acute activation of many transcription factors in patients with severe infection and is a poor prognostic sign in case of severe infection. Uric acid is significant pro inflammatory substance in the pathogenesis of sepsis. Allantoin is the end product of purine metabolism in animals whereas uric acid in human beings. Purines can be endogenous or exogenous. Purines are nitrogenous Compounds found in the body as well as food as end product of purine metabolism, Uric acid passes through the liver, enters the blood stream and most of it excreted in Urine [11, 12]. Some uric acid is degraded in the body after reaction with oxidants. Over the Last ten years, strong association has been found between hyperuricemia with HTN [12], DM [13], Metabolic syndrome [14], stroke [15, 16], CKD [17], CAD [18]. Chronic conditions is also associated with elevated serum uric acid.

Hyperuricemia is defined as serum uric acid > 6.8 mg/dl in males and females [19] as mentioned above uric acid which is a routinely done investigation can predict the prognostic outcome in a multifactorial syndrome like sepsis. Hence this study was conducted to bring out the correlation between Hyperuricemia in clinically diagnosed sepsis patients and its prognostic outcome. We compared relation between hyperuricemia and prognostic indicators of sepsis
Including AKI, ARDS and ICU stay.

2. Materials & Methods

Study Setting: ICU In Shri Balaji Institute Of Medical Sciences, Raipur, Chhattisgarh

Study Population: The present study is conducted on patients admitted in Inpatient department of GENERAL MEDICINE.

Study Design: Prospective Observational Study

Study Duration: FEB 2020 to March 2022, (25months).

Study Criteria:

Inclusion Criteria:
- Age more than 18 years
- Admission to ICU with a working diagnosis of sepsis

Exclusion Criteria:
- Patients denying consent
- Pregnant females
- Known case of chronic kidney disease
- Patients who have already been in ICU in an outside facility for more than 24hrs
- Patients who are known case of gout
- Patients on drugs causing hyperuricemia [15]

Sample Size:
According to the study by Akbar et al [16], the prevalence of hyperuricemia

Patients with sepsis in the MICU at 72 hours was 64.8%
Hence P=64.8%=0.648
1.96= z value for 95% significance level
e= Allowable error =0.10

Cochran formula for a Prospective Observational study.

Minimum Sample Size =N = 1.962 x P x 1-Pe2= 1962 x 0.648 x 1-0.6480.102=88 ICU patients with sepsis which is approximated to 100.

Methods
The present study is conducted on patients admitted at SHRI BALAJI INSTITUTE OF MEDICAL SCIENCES. This was a prospective observational study with 100 patients with diagnosis of sepsis based on qSOFA score. Once the patient meet the inclusion criteria, consent was obtained from the study participants and patients were interviewed for demographic data such as age and sex, history of other comorbid conditions along with presenting complaints were noted. Further these patients were subjected to a physical examination. Blood samples were obtained for uric acid, urea, creatinine, complete blood count, serum electrolytes, ABG and chest X-ray and were taken. These findings were recorded on a predesigned and pretested preformat. Patient was followed throughout the course in the hospital till the outcome.

Statistical Analysis-Data Entry was done using Microsoft excel 2013 and analysis done using SPSSV 16. Qualitative data was expressed in frequencies and percentages and Quantitative Data in mean and standard deviation. Parametric tests include unpaired t test for intergroup comparison was used. Receiver operative curve (ROC) analysis was done to predict the cut off value of Uric acid to predict outcome. Sensitivity and specificity were calculated based on cut off values. Bar diagrams and pie chart were used to represent the data. P value of <0.05 was considered statistically significant.

Ethical Considerations-All patients included in the study were provided with Patient Information Sheets in a language they can understand. All patients were included in the study only after obtaining informed and written Consent. There was no unnecessary cost escalation for the patients. Confidentiality was strictly maintained. Information obtained from this study was used to benefit other Patients in the future.

3. Result

In the present study, out of 100 patients, majority (59%) patients had uric acid Levels less then ≤6.8 mg/dl. **41% patients had higher then>6.8 mg/dl.**

Mean uric acid level of the patients were 6.20±1.60 mg/dl. Out of 100 patients, more than half (55%) of patients were from age group 51 to 70 years followed by 30% from age group 31 to 50 years. Mean age of the patients was 55.02±15.44 years.

Out of 59 patients with uric acid levels ≤6.8 mg/dl, majority (51%) were from age group 51 to 70 years and similarly, out of 41 patients with uric acid levels >6.8 mg/dl, majority (61%) were from age group 51 to 70 years. Distribution was Comparable in both groups and no difference was observed (p value 0.54). In the present study, there was slight **male preponderance**. Out of 100 patients, 54% were males and 46% were females. Male to female ratio was 1.2:1.

Out of 59 patients with uric acid levels ≤6.8 mg/dl, majority (52.5%) were Females and out of 41 patients with uric acid levels >6.8 mg/dl, majority (54%) were Males but this difference was not significant (p value 0.11).

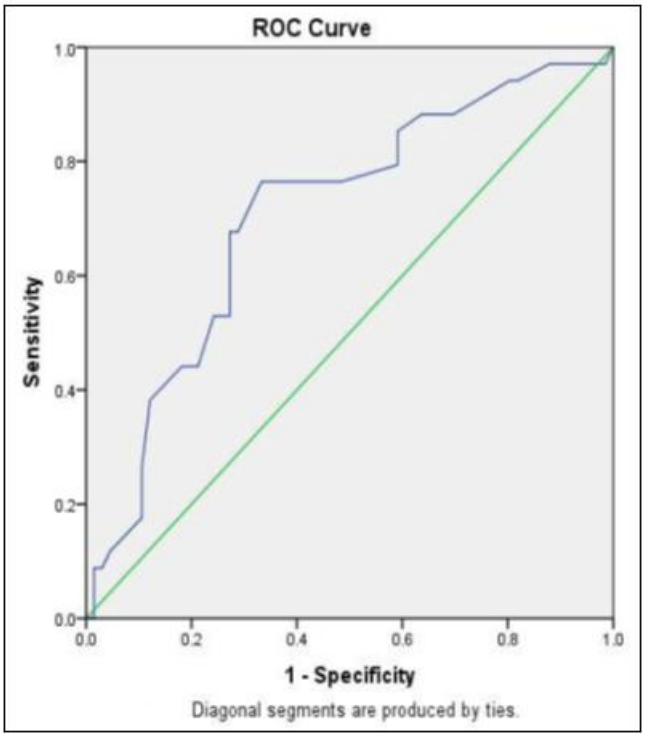
Out of 100 patients, 40% patients were having Type 2 diabetes Mellitus, out of which 13 have associated Hypertension and one had malignancy. Second most common comorbidity was Hypertension in 13% patients. Maximum Uric acid level (9.0mg/dL) was observed in patients with T2DM with Malignancy followed by patients with decompensated chronic liver disease (DCLD) who had uric acid level of 8.04 ±0.390 mg/dL. Uric acid level was minimum (4.40 mg/dL) in patients with hypertension and low (6.01 ±1.54 mg/dL) in patients without any co-morbidities.

Out of 59 patients with uric acid levels ≤6.8 mg/dl, majority (59.3%) stayed in Hospital for < 72 hrs and out of 41 patients with uric acid levels >6.8 mg/dl**, majority (87.8%)** stayed in hospital for ≥72 hrs and **this association between higher uric acid Levels and longer duration of stay was statistically significant (p value 0.0001).**

Out of 100 patients, 33% patients developed Acute Kidney Infection (AKI) Followed by 24% patients developed Acute Respiratory Distress Syndrome (ARDS) and 22% developed AKI associated with ARDS. 21% patients didn't develop any Complications.

Out of 59 patients with uric acid levels ≤6.8 mg/dl, majority (59.3%) didn't Develop AKI and out of 41 patients with uric acid levels >6.8 mg/dl, majority (78.1%) Developed AKI and this **association between higher uric acid levels and development Of AKI was statistically significant** (p value 0.0002).

Out of 59 patients with uric acid levels ≤6.8 mg/dl, majority (81.4%) discharged and out of 41 patients with uric acid levels >6.8 mg/dl, 23 patients died. Proportion of mortality was significantly high in patients with higher uric acid levels and this association between higher uric acid levels and mortality was statistically Significant (p value <0.001). Prognostic value of uric acid levels to predict outcome of sepsis:



For prediction of mortality, AUC for uric acid was 0.707 which was statistically Significant (p value 0.001). It has Sensitivity of 76.5% and Specificity of 66.7% for cut-off Value of 6.60 mg/dL

Correlation between uric acid levels and duration of hospital stay: Correlation coefficient (r2) 0.0303, P value 0.764 There was positive correlation between uric acid levels and duration of hospital Stay (correlation coefficient 0.030) but this correlation was not statistically significant
(p value 0.764).

4. Discussion

Sepsis is one of the most commonly encountered entity in ICU. Over the course of hundreds of years, the meaning of sepsis has evolved. With the progress in the Medicine research, diagnosis of sepsis has become more prevalent. Today, various Biomarkers are employed to aid in the diagnosis and prognosis of sepsis. One such biomarker is uric acid, which is routinely measured in ICU settings Due to its substantial prognostic value. Elevated uric acid levels have been linked to increased mortality and morbidity in sepsis patients, highlighting its importance in Clinical assessments. In our study, we evaluated 100 sepsis patients to investigate the relationship between uric acid levels and patient outcomes, focusing on mortality and morbidity.

We specifically assessed the development of Acute Kidney Injury (AKI), Acute Respiratory Distress Syndrome (ARDS), and the duration of ICU stays as indicators of Morbidity. Our findings underscore the critical role of uric acid as a prognostic marker in Sepsis, providing valuable insights for the management and treatment of this severe Condition.

1. Distribution based on uric acid level in the present study, 41% of the 100 sepsis patients exhibited hyperuricemia, Defined as a serum uric acid level exceeding 6.8 mg/dl. The

mean uric acid Concentration among these patients was 6.2 ± 1.6 mg/dl. This prevalence is slightly Higher than those reported by Akbar et al. [21] (37.5%) and Bhargava et al. [22] (42.7%). [23].

Regarding age distribution, the majority (55%) of all sepsis patients in our study were between 51 and 70 years old. Notably, this age group also constituted the largest Proportion (61%) of hyperuricemia individuals. However, this differs from the findings Of Akbar et al. [21], where the 30-65 age group represented the majority (53.5%) of all Sepsis patients, and 30% of those with hyperuricemia. In contrast, younger patients (31-50 years) comprised a smaller proportion (21.9%) of hyperuricemia patients in our Cohort.

2. Gender Distribution

In our study cohort, the gender distribution among sepsis patients was relatively Balanced, with 54 males (54%) and 46 females (46%). However, among those with Hyperuricemia, there was a notable male predominance, with 26 male patients (63.4%) And 15 female patients (36.6%). This is consistent with the findings of Akbar et al. [21], who reported 57.4% male and 42.6% female hyperuricemia patients. Bhargava et al. [22] observed a more even gender distribution, with 52% male and 48% female hyperuricemia patients.

Distribution based on stay in the ICU In our study, a significant association was observed between hyperuricemia and Prolonged ICU stay in sepsis patients. Out of 41 patients with hyperuricemia, 36 (87.8%) experienced an ICU stay exceeding 72 hours. This finding was statistically Significant, suggesting that hyperuricemia is a potential risk factor for extended ICU Stays in this patient population.

Our results are consistent with previous research. Bhargavi et al. [22] reported a statistically significant association between hyperuricemia and ICU stays longer than Three days, with 54.7% of hyperuricemia patients experiencing prolonged ICU stays. Similarly, A.H. Bhat et al. [19] found a significant association between hyperuricemia and extended ICU stays, reporting a median ICU stay of eight days for hyperuricemia Patients. Taken together, these findings suggest that hyperuricemia may be a valuable Predictor of ICU length of stay in sepsis patients.

Further research is needed to explore The underlying mechanisms of this association and to determine whether interventions Aimed at lowering uric acid levels could potentially reduce the duration of ICU stay in This patient population.

Distribution based on association between uric acid levels and co Morbidities In our study, a significant association was observed between hyperuricemia and several comorbidities, including coronary artery disease (CAD), cerebrovascular Accident (CVA), decompensated chronic liver disease (DCLD), metabolic syndrome (Diabetes mellitus + hypertension), and diabetes mellitus with malignancy. These Findings align with those of Bhardwaj et al. [25], who also identified diabetes mellitus, Decompensated liver disease, and cerebrovascular accident as prevalent comorbidities. In hyperuricemia patients. However, Akbar et al. [21] despite noting a high prevalence Of diabetes mellitus, CAD, congestive heart failure (CHF), and CVA in hyperuricemia Patients, did not find a statistically significant association between these comorbidities and hyperuricemia. Distribution 0f Hyperuricemia and AKI [20]

In our study, a significant association was observed between hyperuricemia and the development of AKI during ICU stays. Of the 41 patients with hyperuricemia, 32 (78%) developed AKI. These findings corroborate existing research, highlighting the link between Hyperuricemia and AKI. Akbar et al. [21] reported a comparable incidence of 68.5% Hyperuricemia in their AKI cohort, while Bhargavi et al. found that 75% of their Hyperuricemia patients developed AKI. Additionally, a study by R. Ughreja et al. [27] demonstrated a significant association, with 77% of sepsis patients developing AKI.

ARDS with hyperuricemia

In our study cohort of 100 sepsis patients, 46 individuals developed Acute Respiratory Distress Syndrome (ARDS) during their ICU stay. Among these, 15 Patients (32.6% of all ARDS patients) also presented with hyperuricemia. This Represents a significant proportion (36.5%) of the 41 patients with hyperuricemia in our Study.

However, despite this considerable overlap, our analysis did not reveal a statistically significant association between hyperuricemia and ARDS ($p = 0.170$).This observation aligns with the findings of Akbar et al. [21], who similarly reported a notable, yet statistically insignificant, prevalence of ARDS among their Hyperuricemia cohort. While both studies suggest a potential link between these Conditions.

Further research with larger sample sizes may be necessary to definitively establish or refute a statistically significant association between hyperuricemia and the Development of ARDS in sepsis patients.

In our study, a total of 23 patients out of the 100 diagnosed with sepsis Succumbed to complications, resulting in a mortality rate of 23%. Notably, 23 out of The 41 patients with hyperuricemia (56%) died, indicating a significantly higher Mortality rate in this subgroup ($p < 0.05$). This finding underscores a strong association between hyperuricemia and increased mortality risk in sepsis patients.

Our results are consistent with previous research, Bhardwaj et al. [23] also demonstrated a statistically significant association between hyperuricemia and Increased mortality in sepsis. Additionally, a study by D.A. Moubarez [28] further supports this link, highlighting the high predictive value of uric acid levels for mortality Risk in sepsis. Bhargavi et al. similarly reported a significant increase in mortality Associated with hyperuricemia in their cohort of sepsis patients.

Taken together, these findings consistently demonstrate that hyperuricemia is a significant risk factor for mortality in sepsis. This suggests that uric acid levels could potentially serve as a valuable prognostic marker and therapeutic target in the Management of sepsis.

5. Conclusion

This study reinforces the critical role of uric acid as a prognostic biomarker in Sepsis. Our findings indicate that elevated uric acid levels are not merely a consequence of sepsis but are significantly associated with adverse outcomes, including prolonged ICU stays, increased risk of acute kidney injury, and higher mortality.

The association between hyperuricemia and increased mortality is particularly Noteworthy, as it suggests that uric acid could serve as a valuable prognostic marker for identifying high-risk sepsis patients. Additionally, the strong link between Hyperuricemia and the development of acute kidney injury underscores the potential for Targeted interventions aimed at lowering uric acid levels to improve outcomes in this Population.

While our study did not find a statistically significant association between Hyperuricemia and acute respiratory distress syndrome, the observed trend warrants further investigation with larger sample sizes. Future research should also focus on elucidating the underlying mechanisms linking uric acid to adverse outcomes in sepsis.

This could pave the way for the development of novel therapeutic strategies that target Uric acid metabolism to improve survival rates and reduce morbidity in sepsis patients.

In conclusion, this study adds to the growing body of evidence supporting the Prognostic significance of uric acid in sepsis.

By identifying hyperuricemia as a key risk factor, clinicians can better stratify patients, tailor treatment plans, and potentially improve outcomes in this life-threatening condition.

References

[1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS. The Third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama. 2016 Feb 23; 315(8):801-10. 13. Spaulding AR, Salgado-Pabón W, Kohler PL, Horswill AR, Leung DY,

[2] Schlievert PM. Staphylococcal and streptococcal superantigen exotoxins.Clinical microbiology reviews. 2013 Jul; 26(3):422-47. 31.

[3] Thomas-Rüddel DO, Hoffmann P, Schwarzkopf D, Scheer C, Bach F, Komann Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of Sepsis: time for a reappraisal. Critical Care. 2020 Dec; 24:1-5.

[4] Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an Activation of the renin–angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. Journal of hypertension. 2010 Jun 1; 28(6):1234-42.

[5] Kadowaki D, Sakaguchi S, Miyamoto Y, Taguchi K, Muraya N, Narita Y, Sato K, Chuang VT, Maruyama T, Otagiri M, Hirata S. Direct radical scavenging activity of benzbromarone provides beneficial antioxidant properties for Hyperuricemia treatment. Biological and Pharmaceutical Bulletin. 2015 Mar 1; 38(3):487-92.

[6] Braga TT, Foresto-Neto O, Camara NO. The role of uric acid in inflammasome-mediated kidney injury. Current opinion in nephrology and hypertension. 2020 Jul 1; 29(4):423-31.

[7] Liu S, Zhong Z, Liu F. Prognostic value of hyperuricemia for patients with sepsis in the intensive care unit. Scientific reports. 2022 Jan 20; 12(1):1070.

[8] Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated Oxidative/nitrosative stress. American Journal of Physiology-Cell Physiology. 2007 Aug; 293(2):C584-96.

[9] Larsen FF, Petersen JA. Novel biomarkers for sepsis: A narrative review.European journal of internal medicine. 2017 Nov 1; 45:46-50.

[10] Shankar-Hari M, Phillips G, Levy M. Assessment of definition and clinical criteria for septic shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama. 2016 Feb 23; 315(8):801-10.

[11] Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, Schuler G, Coats AJ, Anker SD, Hambrecht R. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemia patients with chronic heart failure: results from 2 placebo controlled studies. Circulation. 2002 Jun 4; 105(22):2619-24.

[12] Edwards NL. The role of hyperuricemia and gout in kidney and cardiovascular disease. Cleveland Clinic journal of medicine. 2008 Jul 1; 75: S13-6.

[13] Wang J, Qin T, Chen J, Li Y, Wang L, Huang H, Li J. Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. PloS one. 2014 Dec 1; 9(12):e114259.

[14] Jia Z, Zhang X, Kang S, Wu Y. Serum uric acid levels and incidence of impaired Fasting glucose and type 2 diabetes mellitus: a meta-analysis of cohort studies. Diabetes research and clinical practice. 2013 Jul 1; 101(1):88-96.

[15] Goli P, Riahi R, Daniali SS, Pourmirzaei M, Kelishadi R. Association of serum uric acid concentration with components of pediatric metabolic syndrome: A systematic review and meta-analysis. Journal of Research in Medical Sciences.2020 Jan 1; 25(1):43.

[16] Li M, Hou W, Zhang X, Hu L, Tang Z. Hyperuricemia and risk of stroke: a systematic review and meta-analysis of prospective studies. Atherosclerosis. 2014 Feb 1; 232(2):265-70.

[17] Ji X, Leng XY, Dong Y, Ma YH, Xu W, Cao XP, Hou XH, Dong Q, Tan L, Yu JT. Modifiable risk factors for carotid atherosclerosis: a meta-analysis and Systematic review. Annals of translational medicine. 2019 Nov; 7(22).

[18] Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset

chronic kidney disease? A systematic review and met analysis based on observational cohort studies. BMC nephrology. 2014 Dec; 15:1-2.

[19] Yu W, Cheng JD. Uric acid and cardiovascular disease: an update from molecular mechanism to clinical perspective. Frontiers in pharmacology. 2020 Nov 16; 11:582680.

[20] Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL.Harrisons principles of internal medicine. InHarrisons principles of internal medicine-21 st edition 2022 (pp. 3249-3249).

[21] Akbar SR, Long DM, Hussain K, Alhajhusain A, Ahmed US, Iqbal HI, Ali AW,Leonard R, Dalton C. Hyperuricemia: an early marker for severity of illness in Sepsis. International journal of nephrology. 2015; 2015(1):301021.

[22] Bhargavi Sindhuja N. *A Study on Hyperuricemia as an Early Marker for Severity of Illness in Sepsis in IMCU of a Tertiary Care Centre* (Doctoral dissertation, Government Vellore Medical College, Vellore). Bhardwaj B, Gupta S, Garg S. ESTIMATION OF THE URIC ACID LEVEL FOR THE ASSESSMENT OF THE SEVERITY OF DISEASES WITH CLINICALLY DIAGNOSED SEPSIS. Int J Acad Med Pharm. 2023; 5(3):159-62.

[23] Bhat AH. Uric acid a predictor of sepsis in critically ill patients. Journal of Advanced Medical and Dental Sciences Research. 2018 Jan; 6(1).

[24] Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. Jama. 1993 Dec 22; 270(24):2957-63.

[25] Ughreja R. Analysis of uric hyperuricemia as early indicator of illness in sepsis condition.

[26] Moubarez DA. The predictive value of serum uric acid in development of acute kidney injury and mortality in patients with sepsis. Journal of Nephropathology.2022 Apr 1; 11(2).

[27] Wagner D, Draper E, Knaus W. Development of Apache III. Critical care medicine. 1989 Dec 1; 17(12 PART 2):S199-203.